Genetics of Parkinson's disease

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Outline

Defining the research question……PD

Rare variants (genome-wide linkage)

Common variants (GWAS)

What lies in between…

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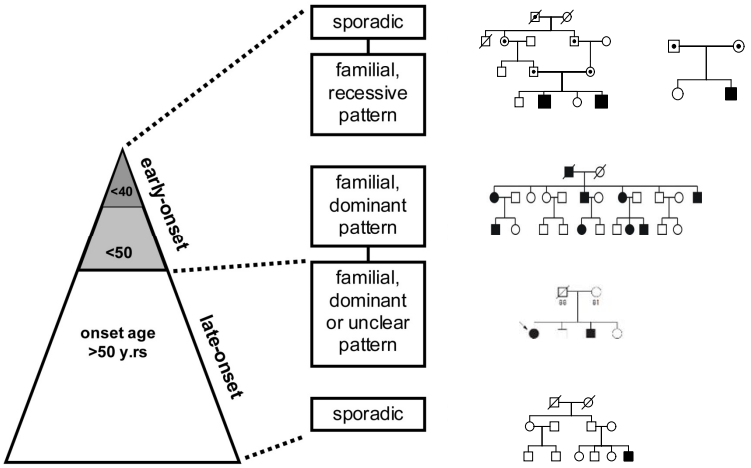
Clinical Genetics of PD

- familial in ~15% of cases (Mendelian pattern rarely evident)
- early-onset (<45 y.rs) in ~5-10% of cases



Adapted from: Bonifati, Genetics of parkinsonism.
In: Wood (Ed.) Neurogenetics – a guide for clinicians. Cambridge Univ Press 2012

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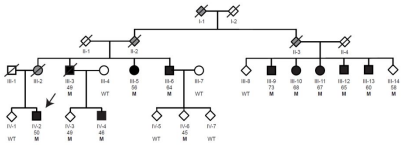
genome-wide linkage
family-based



the yield:

- rare variants
- large effect size

(highly-penetrant, disease-causing)

rare, but possible crucial insights
into disease mechanisms

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Monogenic parkinsonisms

Lewy bodies+ pathology

autosomal dominant

PARK1
SNCA / α-synuclein

PARK8
LRRK2 / dardarin

PARK17 / VPS35

CHCHD2

LRP10

autosomal recessive

PARK2 / parkin

PARK6 / PINK1

PARK7 / DJ-1

VPS13C

PARK9 / ATP13A2

PARK14 / PLA2G6

NBIA4 / MPAN (c19orf12)

PARK15 / FBXO7

PARK19 / DNAJC6 (auxilin)

PARK20 / SYNJ1 (synaptojanin-1)

PTRHD1

Variable penetrance (usually low)

GBA / glucocerebrosidase

X-linked recessive
X-linked dominant

RAB39B

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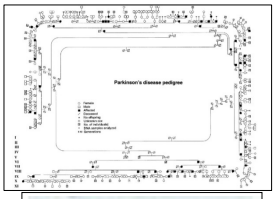
PARK1 - *α-synuclein*

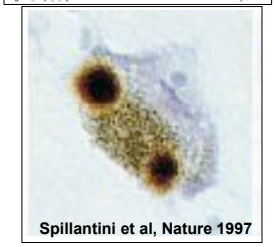
Polymeropoulos et al, Science 1997



proof-of-principle - monogenic cause of PD with Lewy-body pathology

- missense mutations

- gene duplication
- gene triplication
(Singleton et al, Science 2003)



Spillantini et al, Nature 1997

α-syn in Lewy bodies : PD, LBD, MSA as "synucleinopathies"

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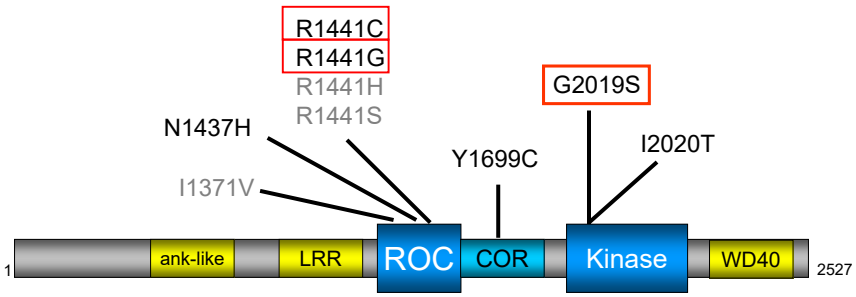
PARK8 – *LRRK2* Leucine-Rich Repeat Kinase 2

PD-causing mutations



Zimprich et al, 2004
Paisan-Ruiz et al., 2004

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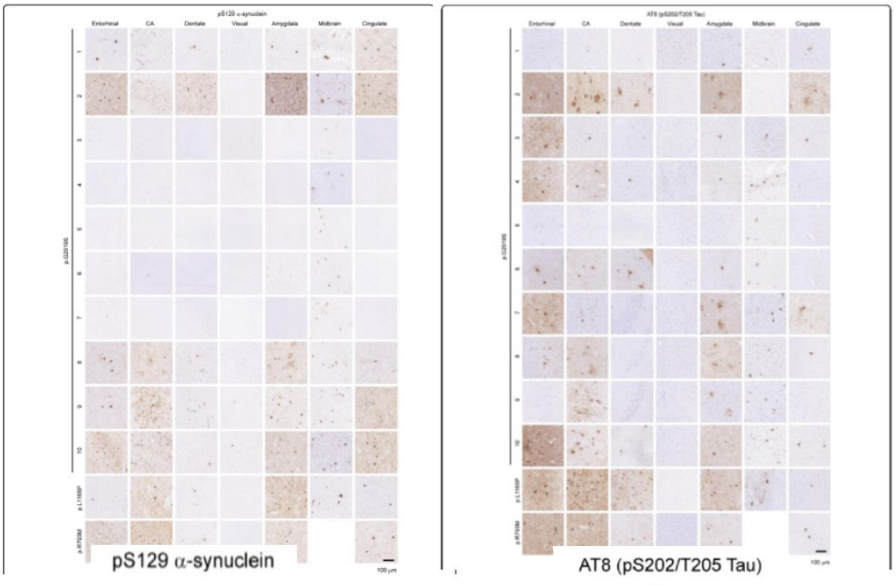
Alzheimer's disease tau is a prominent pathology in LRRK2 Parkinson's disease

Henderson et al.
Acta Neuropathol Com 2019



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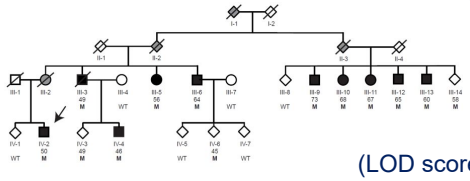
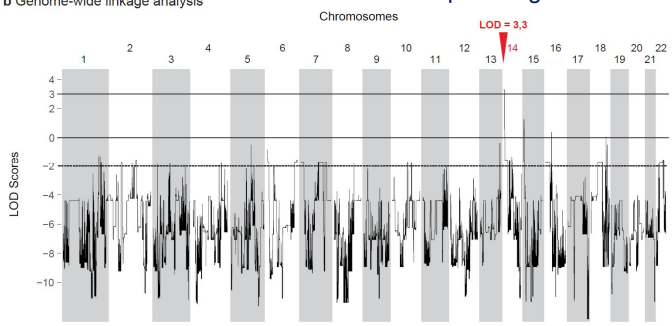
LRP10 genetic variants in familial Parkinson's disease and dementia with Lewy bodies: a genome-wide linkage and sequencing study

Quadri et al.
Lancet Neurology
July 2018



(LOD score 3.3)
p<0.05 genome-wide



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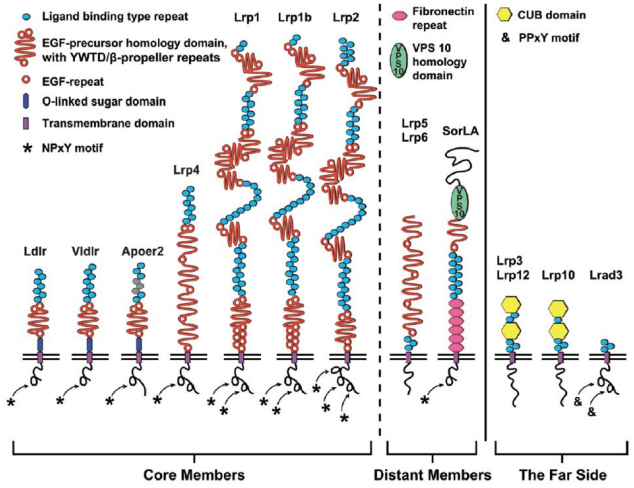
The low-density lipoprotein (LDL) receptor family



Pohlkamp et al., Front. Mol. Neurosci. 2017

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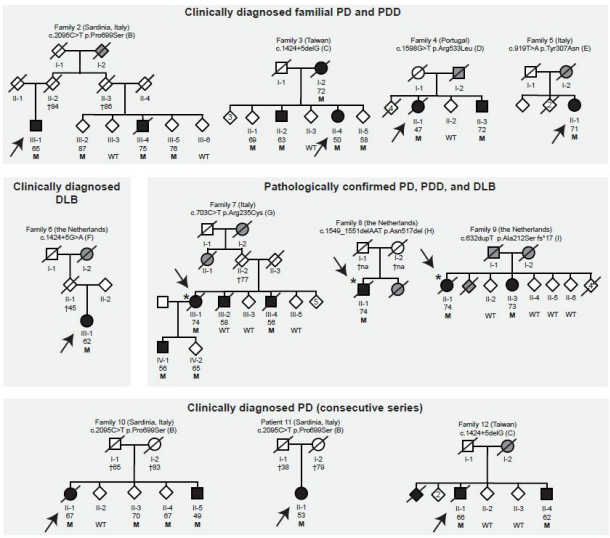
Figure 2

a Pedigrees of additional *LRP10* variant carriers



Stage 2+3:

11 families
8 variants

Cosegregation 9/10
additional affected relatives

Quadri et al., Lancet Neurology, July 2018

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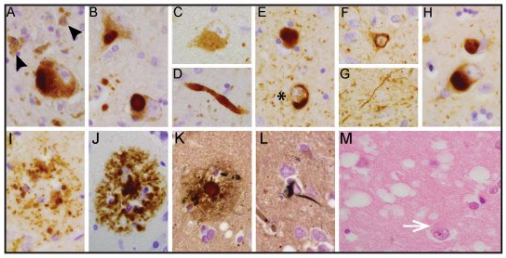
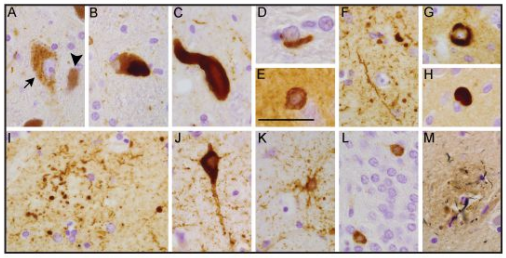
Figure 3

Brain pathology in 3 patients with *LRP10* variants

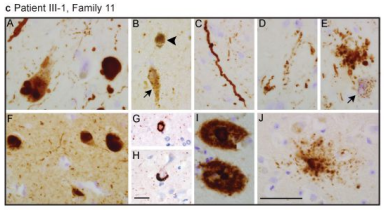
a Patient II-1, Family 12



b Patient II-1, Family 13



c Patient III-1, Family 11



Quadri et al., Lancet Neurology, June 7, 2018

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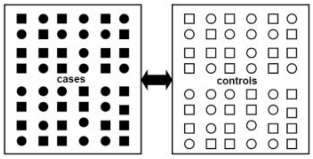
genome-wide association (GWAs) case-control design



the yield (so far):

- common variants
- small effect size

(OR <2, disease risk modulation)

Insights into disease mechanisms

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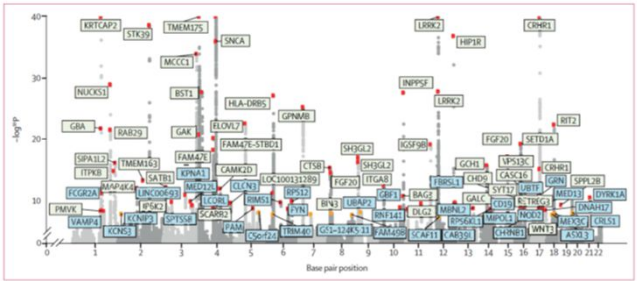
Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies

Nalls et al., Lancet Neurol 2019



meta-analysis of 17 datasets from Parkinson's disease GWAS
7·8 million SNPs, **37.688 cases**, **18.618 UK Biobank proxy-cases** (subjects who do not have PD but have a 1st degree relative with PD), and **1·4 million controls**

Yield: 90 risk variants in 78 genomic loci, **38 novel (but with OR~1,06)**
estimated to explain **16–36% of the heritable risk** for PD
heavily **brain-enriched** loci (gene expr.), and **neuronal** (not glial)

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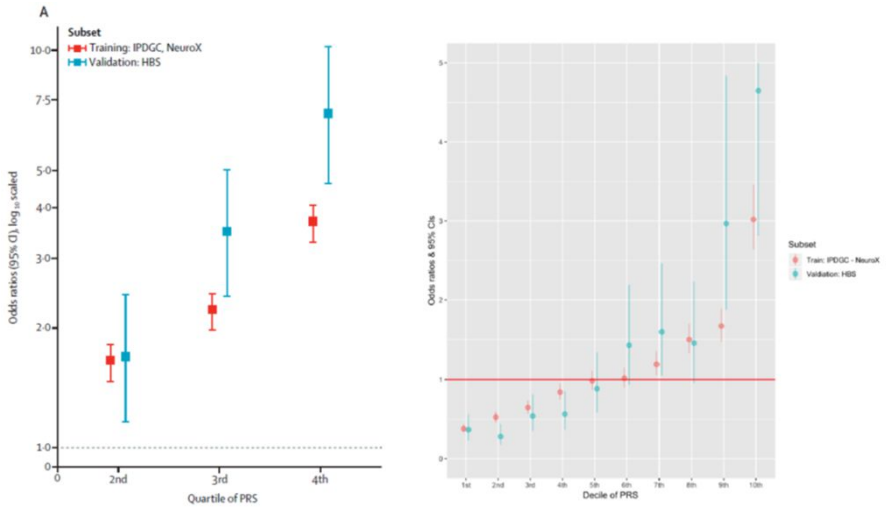

Nalls et al., Lancet Neurol 2019

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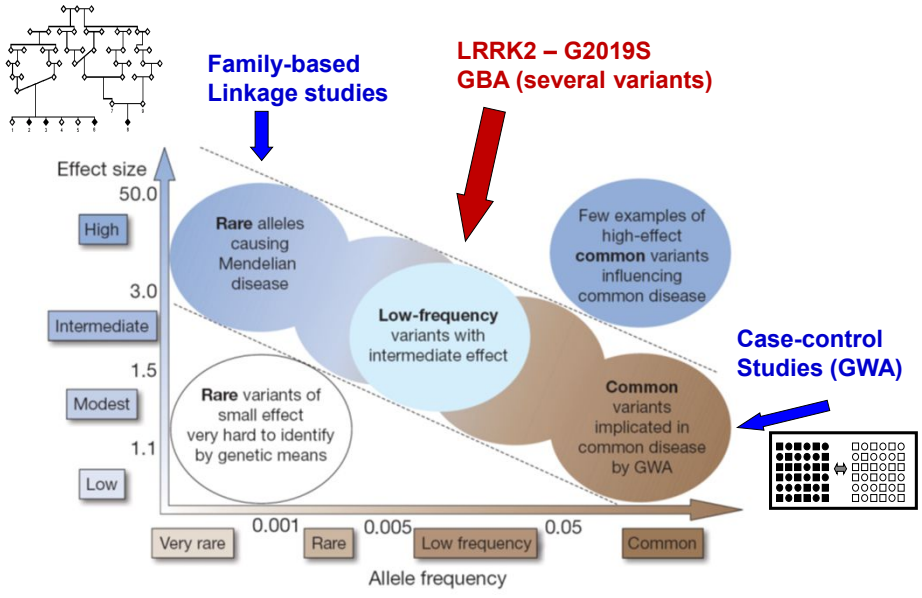

Adapted from Manolio et al, Nature 2009

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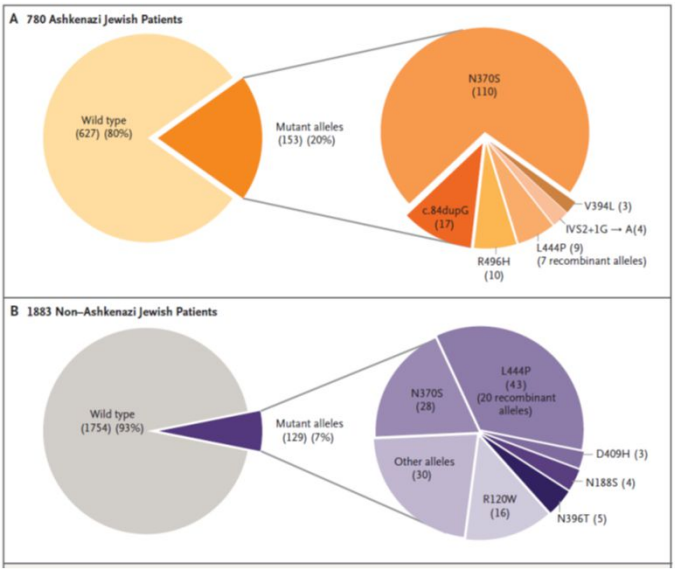
GBA

OR 5.43 (cumulative estimate, any GBA variant)



Sidransky et al., N Engl J Med 2009

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GBA

Highly-homologous pseudogene – challenging assay

Many variants, including novel and very rare

Different size-effects (OR: <3 to >10)

Low-penetrance “cause” vs strong “risk factor”

N370S – most common variant in AJ patients

L444P – most common variant in non-AJ patients

Several complex alleles (recombinant)

Genotype-phenotype correlations emerging

Clinical Trials on PD-GBA carriers ongoing

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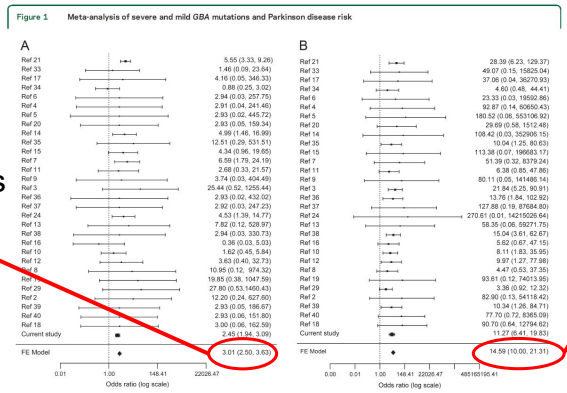
Differential effects of severe vs mild *GBA* mutations on Parkinson disease

Gan-Or et al., Neurology 2015

1000 Ashkenazi-Jewish PD, 3805 controls; screened for 7 GBA mutations
19.2 % (n=192) among PD; 6.4 % (n=242) among controls
meta-analysis: 11453 PD, 14565 controls



mild mutations OR = 3

severe mutations OR = 14.6

GBA mutations: similar mechanisms in Gaucher and PD
(loss-of-function hypothesis)

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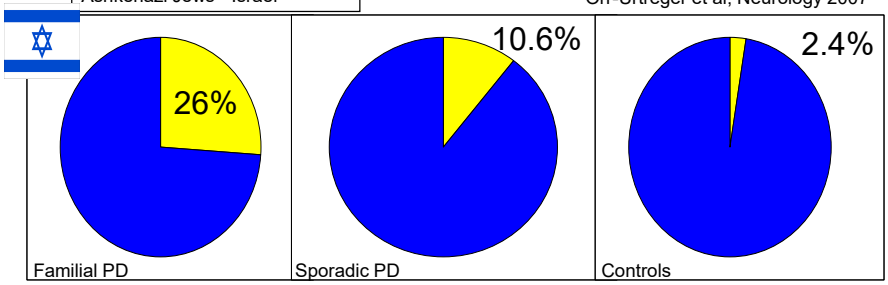
Gly2019Ser

Reduced penetrance (several studies)
as low as ~20% in some studies

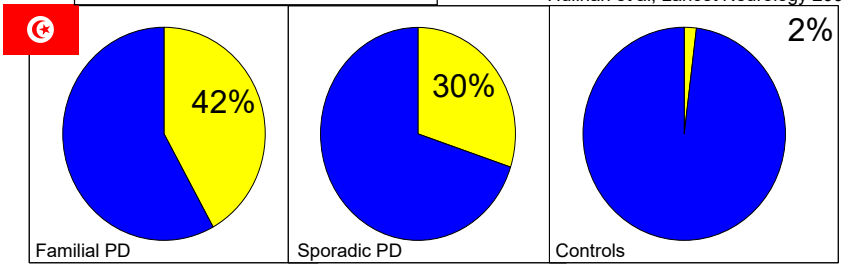
Ashkenazi Jews - Israel

Orr-Urtreger et al, Neurology 2007



Arab-Berber Tunisia

Ishihara et al, Mov Disord 2006
Hulihan et al, Lancet Neurology 2008



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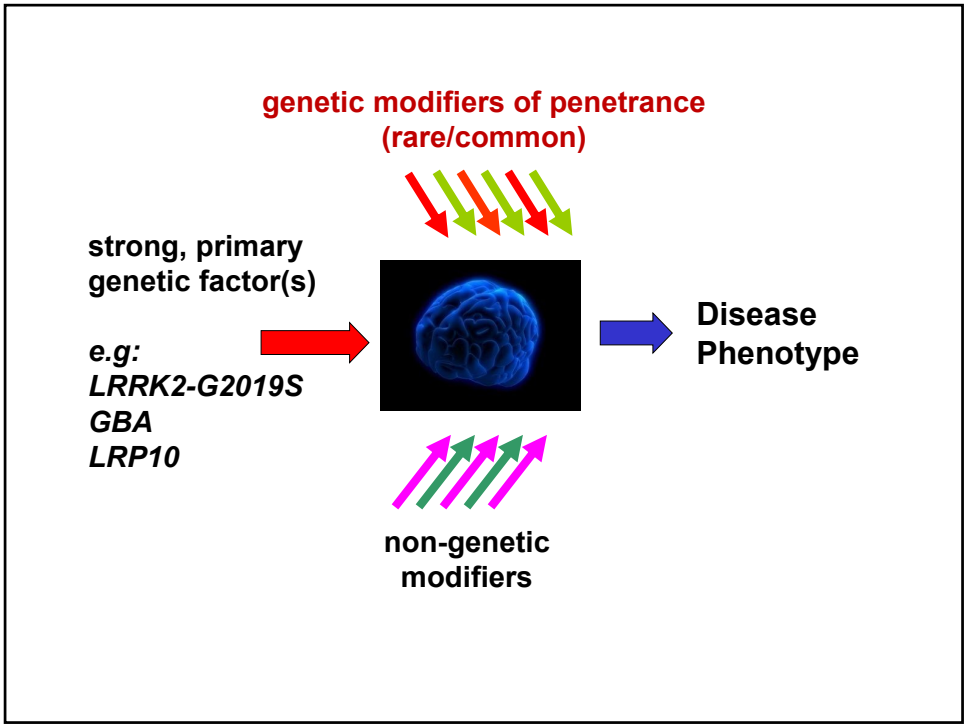

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Resistance to autosomal dominant Alzheimer's disease in an *APOE3* Christchurch homozygote: a case report

Arboleda-Velasquez et al., Nat Med 2019

Presenilin 1 mutation carrier from the world's largest autosomal dominant Alzheimer's disease kindred, who did not develop mild cognitive impairment until her seventies, three decades after the expected age of clinical onset

The individual was homozygous for **APOE3 Christchurch** (R136S) mutation (LOF), unusually **high brain amyloid levels** and limited tau and neurodegenerative measurements

Implications for the role of APOE in the pathogenesis, treatment and prevention of Alzheimer's disease

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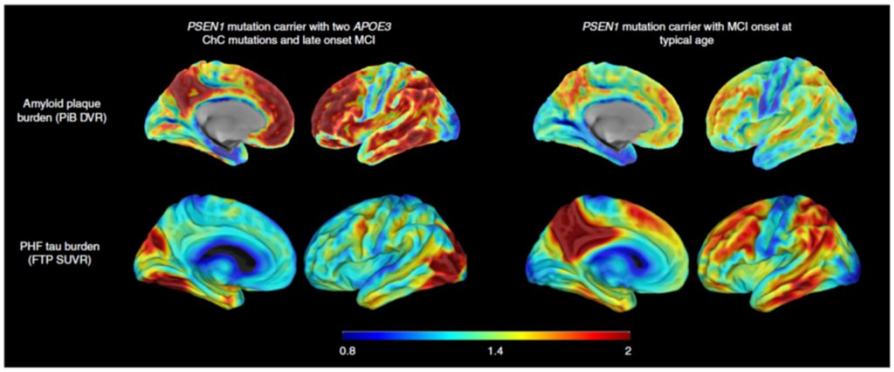
Resistance to autosomal dominant Alzheimer's disease in an *APOE3* Christchurch homozygote: a case report

Arboleda-Velasquez et al., Nat Med 2019

very high brain amyloid levels,
limited tau and neurodegenerative measurements



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Key points



From the etiological standpoint: there are many types of PD

- Mutations in several genes can cause PD
- Variable role for genetic and non-genetic factors in diff. patients
- Genetic architecture of PD differs between populations

α-synuclein : 1st proof-of principle – (rare) monogenic cause LB+ PD

LRRK2* and *GBA : **low-penetrant mutations** (strong PD risk factors)
common (in some populations very common !)
link pathogenesis of familial and sporadic PD
→ **disease-modifying intervention trials**

Early-onset PD : several monogenic forms (rare) (recessive)
links to late-onset PD unclear

Other genes for early and late-onset PD probably remain to be identified !

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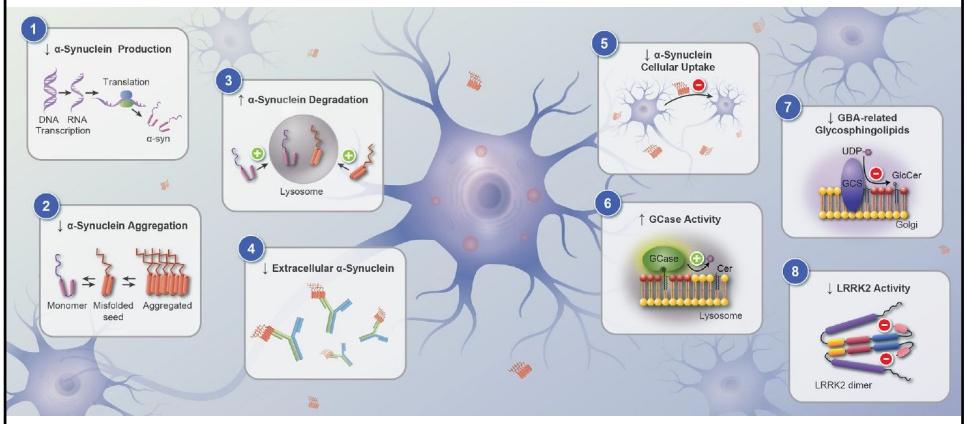
Where are the therapies ?



Sardi et al., Mov Disord 2018

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STICHTING ParkinsonFonds
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